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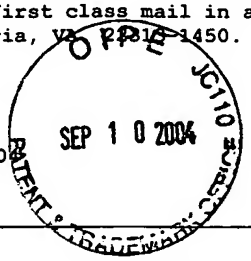

Kimberly J. Prior
(Print Name)

Date: September 8, 2004

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1616

Joerg Huwyler, et al.

Serial No.: 10/740,245

Filed: December 18, 2003

For: **OXAZOLES AS mGluR 1 ENHANCERS**

TRANSMITTAL OF CERTIFIED COPY

September 8, 2004

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Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	02028747.0	December 23, 2002

Respectfully submitted,

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Enclosures

Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02028747.0

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02028747.0
Demande no:

Anmeldetag:
Date of filing: 23.12.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

4070 Basel
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Oxazoles as mGluR 1 enhancers

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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C07D413/00

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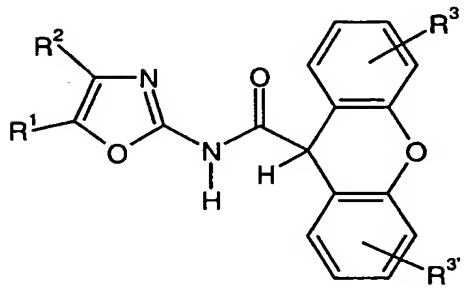
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SI SK

F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 21382

Oxazoles as mGluR 1 enhancers

This invention relates to carboxamide derivatives of the general formula



I

wherein

one of R^1 and R^2 signifies trifluoromethyl, and the other one signifies hydrogen;

R^3, $R^{3'}$ signify, independently from each other, hydrogen or halogen;

as well as their pharmaceutically acceptable salts.

The compounds of formula I are new. They are described generically in PCT patent application No. WO 00/63166 (F. Hoffmann-La Roche AG).

These compounds and their salts are characterized by valuable therapeutic properties. It has surprisingly been found that the compounds of general formula I are mGlu 1 receptor agonists and positive allosteric modulators (enhancers) of metabotropic glutamate 1 (mGlu1) receptors.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluRs) belong to the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present, eight different members of these mGluRs' are known and of these some even have sub-types. On the basis of structural parameters, the different second messager signalling pathways and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:
mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depression.

Indications which are potentially treatable with mGluR1 agonists include Alzheimer's disease, cognitive disorders and memory deficits, Huntington's chorea, amyotrophic lateral sclerosis (ALS), and dementia.

Selective positive allosteric modulators (enhancers) of mGlu1 receptors are compounds which do not directly activate mGlu1 receptors by themselves, but binding of these compounds increase the affinity of a glutamate-site agonist at its extracellular N-terminal binding site. Positive allosteric modulation is an attractive mechanism for enhancing appropiate physiological receptor activation, and the results obtained in cerebellar slices strongly suggest that mGluR1 enhancers can modulate physiological mGlu1 activity in the brain (F. Knoflach et al., *Proc. Nat. Acad. Sci. USA* 2001, 98, 13402-13407) by increasing the affinity of a glutamate-site agonist at its extracellular N-terminal

binding site. Selective mGluR1 enhancers therefore possess important therapeutic utility and their discovery opens the possibility for therapeutically relevant positive modulation of mGlu1 receptors.

The object of the present invention therefore is to provide compounds which must have the advantageous properties mentioned above and are therefore useful in the prevention and treatment of the above mentioned diseases. It has been found that the compounds of formula I and their pharmaceutically acceptable salts show the potential to be mGluR I enhancers. Subjects of the present invention are further a process for the manufacture of such compounds, their use as pharmaceutically active substances, medicaments based on a compound in accordance with the invention and the production of such medicaments.

Preferred compounds of formula I in the scope of the present invention are for example those, wherein R^3 and $R^{3'}$ signify hydrogen.

These are the following compounds:
9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide, and
9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide.

Further preferred compounds of formula I are those, wherein R^1 signifies trifluoromethyl and R^2 signifies hydrogen.

Especially preferred are compounds of formula I, wherein R^1 signifies trifluoromethyl, R^2 signifies hydrogen, and wherein at least one of R^3 or $R^{3'}$ signifies halogen. More preferably, at least one of R^3 or $R^{3'}$ signifies fluoro.

The following compounds are examples thereof:
2-fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide,
3-fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide,
4-fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide,
2,7-difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide, and
3,6-difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide.

Further preferred are compounds of formula I, wherein R^2 signifies trifluoromethyl and R^1 signifies hydrogen.

Especially preferred are compounds of formula I, wherein R^2 signifies trifluoromethyl, R^1 signifies hydrogen, and wherein at least one of R^3 or $R^{3'}$ signifies halogen. More preferably, at least one of R^3 or $R^{3'}$ signifies fluoro.

Examples thereof are the following compounds:
2-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide,
3-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide,
3-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide,
2,7-difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide, and
3,6-difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide.

Also preferred are compounds of formula I, wherein R^2 signifies trifluoromethyl, R^1 signifies hydrogen, and wherein at least one of R^3 or $R^{3'}$ signifies chloro.

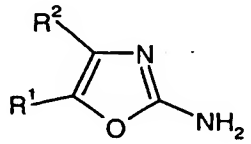
The following compounds are examples thereof:
2-chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide, and
4-chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide.

The invention embraces all stereoisomeric forms in addition to the racemates.

The term "halogen" embraces fluorine, chlorine, bromine and iodine.

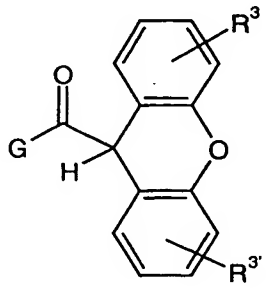
The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by a process, which comprises

reacting a compound of formula



II

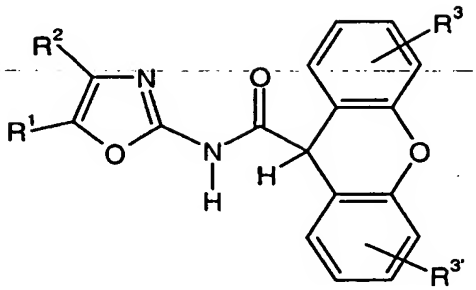
wherein one of R^1 and R^2 signifies trifluoromethyl, and the other one signifies hydrogen, with a compound of formula



III

wherein R^3, $R^{3'}$ signify, independently from each other, hydrogen or halogen, and G signifies chloro or hydroxy,

to obtain a compound of formula

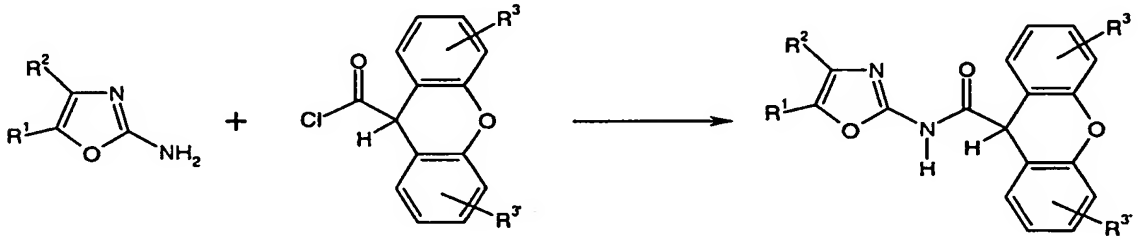


I

and, if desired,
converting a compound of formula I into a pharmaceutically acceptable salt.

In accordance with this process, compounds of formula I may be prepared by a reaction of an oxazol-2-ylamine of formula II with a carboxylic acide chloride of formula IIIa in the presence of N,N-dimethylamino pyridine at a temperature of 0 °C. The preferred solvent is methylene chloride (scheme 1).

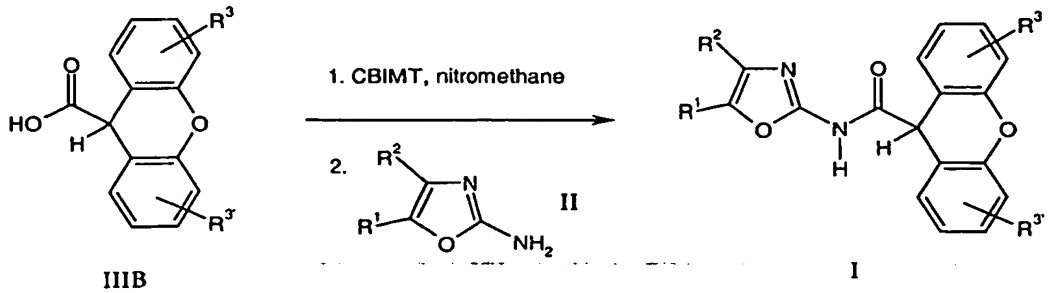
Scheme 1



II IIIa I

Alternatively, compounds of formula I may be prepared by a reaction of an oxazol-2-ylamine of formula II with a xanthene-9-carboxylic acide of formula IIIb. The carboxylic acide is activated with 1,1'-carbonylbis(3-methylimidazolium)triflate (CBMIT) in nitromethane at a temperature of 10 °C. After warming up to room temperature the amine is added (scheme 2).

Scheme 2



IIIB II I

The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation or pharmaceutically acceptable salts of acidic compounds.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, mGluR1 enhancers and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive diorders and memory deficits, as well as acute and chronic pain. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Alzheimer's disease, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

The compounds of the present invention are group I mGlu receptor agonists. The compounds show activities, as measured in the assay described below, of 0.2 μM or less.

In the table below are shown specific EC_{50} values of compounds of formula I:

Example No.	Name	EC_{50} (μM)
1	9H-Xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.056
2	9H-Xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide	0.038
3	(RS)-2-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.055

4	(RS)- 2-Fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide	0.020
5	(RS)-3-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.040
7	(RS)-4-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.016
8	(RS)-4-Fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide	0.021
9	2,7-Difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.044
10	2,7-Difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide	0.124
11	3,6-Difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.003
12	3,6-Difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide	0.025
13	(RS)-2-Chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.015
14	(RS)-4-Chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide	0.093

Test description for binding assay

cDNA encoding rat mGlu 1a receptor obtained from Prof. S. Nakanishi (Kyoto, Japan) was transiently transfected into EBNA cells using a procedure described by Schlaeger et al, New Dev. New Appl. Anim. Cell Techn., Proc. ESACT Meet., 15, (1998), 105-112 and 117 –120. $[Ca^{2+}]i$ measurements were performed on mGlu 1a transfected EBNA cells after incubation of the cells with Fluo-3 AM (0.5 µM final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. $[Ca^{2+}]i$ measurements were done using a fluorometric imaging plate reader (FLIPR, Molecular Devices Corporation, La Jolla; CA; USA). When

compounds were evaluated as antagonists they were tested against 10 μM glutamate as agonist.

The activation (agonists) curves were fitted with a four parameter logistic equation giving EC_{50}, and Hill coefficient using the iterative non linear curve fitting software Origin (Microcal Software Inc., Northampton, MA, USA).

The compounds of formula I of the present invention are further characterized by high metabolic stability. This parameter is a prerequisite for good bioavailability, which is necessary to obtain medicaments with acceptable in-vivo activity. Their metabolic stability has been tested by the following method:

Test description for microsome incubation

Incubation mixtures consisted of liver microsomes (rat 1.0 mg prot/mL or human 2.0 mg prot/mL), test compound 10μM, $MgCl_2$ (3.3 mM), and an NADPH regenerating system consisting of glucose-6-phosphate dehydrogenase, NADPH and glucose-6-phosphate (equivalent to 1 mM NADPH) in a total volume of 1.0 mL of potassium phosphate buffer 100 mM pH 7.4. Reactions were initiated by addition of the NADPH regenerating system at 37 °C. At the time of 1, 5, 9, 13, 17, 21, 25, and 29 min a 5 μL aliquot was directly analysed on a HPLC-MS/MS system consisting of a HP 1100 quaternary pump with degasser and a PE-Sciex API-2000 MS/MS spectrometer. The analytical column was a Waters Symmetry Shield RP8 (2.1*50mm with a 3.5 μM particle size). A polarity non-linear gradient from phase A (MeOH/Ac. Form.1 % 20/80) to phase B (MeOH) was applied for a total run time of 2 minutes at a flow rate of 0.25 mL/min. The PE-Sciex API-2000 MS/MS spectrometer was used for detection of the parent compound. In vivo metabolic clearance was predicted according to published procedures (Houston, J.B., Biochem. Pharmacol. 1994, 47, 1469-1479). In brief, the intrinsic clearance (Clearance, see table below) is calculated from the measured in vitro half-life taking into account incubation volume and microsomal protein used for the in vitro incubation. The intrinsic clearance is expressed in terms of μl/min/mg microsomal protein. For in vivo extrapolations, the hepatic extraction ratio (E) was calculated. Here it is reported the %MAB value which is equal to 1-E. The MAB (maximal achievable bioavailability) values express the maximal bioavailability that one can achieve with the given clearance values.

Example No.	Intrinsic clearance (rat) (µl/min/mg)	MAB (rat)	Intrinsic clearance (human) (µl/min/mg)	MAB (human)
1	108	25 %	8	68 %
2	50	37 %	14	68 %
3	61.4	32 %	9,9	61 %
4	40.2	43 %	18.8	45 %
5	34.3	46 %	4.3	78 %
6	27.8	52 %	9.2	63 %
7	32.8	48 %	7.9	67 %
8	31.8	49 %	19.2	45 %
9	8.9	77 %	2.7	85 %
10	26.1	54 %	5.6	73 %
11	17.6	63 %	11.1	59 %
12	11.6	72 %	9.1	63 %

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Finally, as mentioned earlier, the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind, is also an object of the invention.

Example 1

9H-Xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

a) 4-Trifluoromethyl-oxazol-2-ylamine

The 4-trifluoromethyl-oxazol-2-ylamine is obtained using the procedure described in the literature (G. Crank, M.J. Foulis, J. Med. Chem. 1971, 14(11), 1075).

b) 9H-Xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

To a solution of 150 mg (0.99 mmol, 1.0 equiv.) 4-trifluoromethyl-oxazol-2-ylamine and 6 mg (0.05 mmol, 0.05 equiv.) of N,N-dimethylamino pyridine in 2 ml of dry pyridine is added a solution of 245 mg (0.99 mmol) 9-xanthene-carboxylic acid chloride (CAS: [26454-53-5]) in 2 ml of methylene chloride dropwise at 0 °C. The mixture is stirred 1 h at 0 °C and then at room temperature overnight. The mixture is poured into a well stirred mixture of 30 ml of methylene chloride and 30 ml of water. The organic phase is separated. The aqueous phase is extracted twice with 30 ml of methylene chloride. The combined organic phases are washed with 25 ml of water, dried over magnesium sulfate, and concentrated. The crude product (590 mg, yellow solid) yields, after recristallisation from Ethyl acetate/Hexane 250 mg (0.66 mmol, 66%) of 9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide as white cristals, m.p. 222 °C and MS: m/e = 361.2 ($M+H^+$).

Example 2

9H-Xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

a) 5-Trifluoromethyl-oxazol-2-ylamine

The 5-trifluoromethyl-oxazol-2-ylamine, off-white solid and MS: m/e = 152.0 (M^+), is obtained using the following procedure:
To a solution of 21.6 ml (39.4 g, 0.2 mol) of 97% 3-bromo-1,1,1-trifluoroacetone in 40 ml of tert-butanol are added 12.6 g (0.3 mol, 1.5 equiv.) of cyanamide. A slight exotherm is observed. After stirring for 10 min, 19.7 g (0.24 mol, 1.2 equiv.) of finely powdered sodium acetate were added with vigorous stirring and the suspension is heated for 30 min at 65 °C, refluxed for 2h and then allowed to cool. The mixture is poured into a well stirred mixture of 200 ml of ethyl acetate and 100 ml of water. The pH of the aqueous phase is set to ca. 8-9 with 5% sodium bicarbonate solution. The org. phase is separated. The aqueous phase is extracted with 50 ml ethyl acetate. The combined organic phases were washed twice with 20 ml of water and concentrated in vacuo. The residue, 40.2 g, viscous light orange oil, is then purified by flash chromatography on silica gel using a 2:1 mixture of methylene

chloride and ethyl acetate as eluent. The fractions containing the desired compound (6.08 g, light yellow oil) and containing more polar impurities were concentrated and repurified by flash chromatography on silica gel using a 98:2 mixture of methylene chloride and methanol as eluant. One obtains 1.83 g (0.012 mol, 6%) of 5-trifluoromethyl-oxazol-2-ylamine.

b) 9H-Xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 218 °C and MS: m/e = 360.1(M^+), is prepared in accordance with the general method of example 1b from 5-trifluoromethyl-oxazol-2-ylamine and 9-xanthene-carboxylic acid chloride.

Example 3

(RS)-2-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

a) 2-Fluoro-9H-xanthene

To a solution of 19.63 g 2-fluoro-9-xanthone (CAS: [2839-49-8]) in 290 ml THF were added at room temperature 21.7 ml of Borane dimethylsulfide complex. The mixture is refluxed for 4h, and cooled to 5 – 10 °C. 200 ml of Methanol were added dropwise. An exotherm accompagnied with foam and gas evolution is observed. The solution is evaporated to dryness, taken up in 200 ml of methanol and evaporated to dryness. The residue is taken up in 200 ml of ethyl acetate and evaporated to dryness. The crude product, 18.69 g beige solid, is purified by flash chromatography on silicagel using hexane as eluant. One obtains 17.97 g (89.8 mmol, 98%) of 2-fluoro-9H-xanthene as a white solid.

b) racemic (RS)-2-Fluoro-9-xanthene-carboxylic acid

To a solution of 17.97 g fluoro-9H-xanthene in 285 ml of dry tetrahydrofurane is added at -70 °C to -65° C 53.9 ml of a 2M solution of lithium diisopropylamide. The red solution is stirred for 20 min at –70 °C, and then several pieces of dry ice are added to the mixture at -75 °C. The red color rapidly disappears and the mixture is allowed to warm up to room temperature and stirred for 15 min. 250 ml of water are then added and stirring is maintained another 15 min. Ether (300 ml) is added to the mixture. The organic phase is extracted twice with 100 ml 2N sodium hydroxide solution and washed twice with 50 ml of water. The combined aqueous phases are washed with 25 ml of ether and then the pH is adjusted to 1-2 by addition of 27% hydrochloric acid solution. A white precipitate is formed. The acidified aqueous phase is extracted once with 300 ml of a 9:1 mixture of methylene chloride and methanol 9:1 and twice with 300 ml of methylene chloride. The combined organic phases are washed with 30 ml of water, dried over sodium sulfate and

concentrated in vacuo. The crude product (12.87 g, beige solid) is triturated with ether to yield 11.78 g (48.2 mmol, 54%) of (RS)-2-fluoro-9-xanthene-carboxylic acid as white cristals, neg. ion MS: m/e = 198.9 ($(M-HCO2)^-$).

c) (RS)-2-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

To a solution of 883 mg (1.80 mmol, 1.1 equiv.) of 1,1'-carbonylbis(3-methylimidazolium) triflate (CBMIT) [Saha & al., J. Am. Chem. Soc. 1989, 111, 4856] in 3 ml of nitromethane at 10 °C are added 400 mg (1.64 mmol) of (RS)-2-fluoro-9-xanthene-carboxylic acid. The resulting suspension is allowed to warm up to room temperature and is stirred another 15 min. 4-Trifluoromethyl-oxazol-2-ylamine (274 mg, 1.80 mmol, 1.1 equiv.) is added and the mixture is stirred at room temperature for 16h. The resulting light red viscous mixture is extracted with a mixture of 45 ml methylene chloride, 5 ml of methanol and 50 ml of water. The organic phase is separated. The aqueous phase is extracted twice with 30 ml methylene chloride / methanol 9:1. The combined organic phases are washed with 30 ml of water, dried over sodium sulfate and concentrated in vacuo. The crude product (630 mg, light red solid) is purified by flash chromatography on silicagel using methylene chloride as eluant. One obtains after recristallisation from ethyl acetate/hexane 233 mg (0.62 mmol, 38%) of (RS)-2-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide as a white solid, m.p. 241 °C and MS: m/e = 379.1($M+H^+$).

Example 4

(RS)- 2-Fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

The title compound, light yellow solid, m.p. 217 °C and neg. ion MS: m/e = 377.1 ($M-H^-$), is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and (RS)-2-fluoro-9-xanthene-carboxylic acid.

Example 5

(RS)-3-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

a) (RS)-3-Fluoro-9-xanthene-carboxylic acid

The racemic (RS)-3-fluoro-9-xanthene-carboxylic acid, white solid, neg. ion MS: m/e = 198.9 ($(M-HCO2)^-$), is obtained in accordance with the general method of examples 3a and 3b from 3-fluoroxanthone (CAS:[2839-50-1]).

b) (RS)-3-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

The title compound, light yellow solid, m.p. 221 °C and MS: m/e = 379.1 ($M+H^+$) is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and (RS)-3-fluoro-9-xanthene-carboxylic acid.

Example 6

(RS)-3-Fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 250 °C and neg. ion MS: m/e = 377.1 ($M-H^-$) is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and (RS)-3-Fluoro-9-xanthene-carboxylic acid.

Example 7

(RS)-4-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

a) (RS)-4-Fluoro-9-xanthene-carboxylic acid

The racemic (RS)-4-Fluoro-9-xanthene-carboxylic acid, white solid, neg. ion MS: m/e = 198.9 ($(M-HCO2)^-$) is obtained in accordance with the general method of examples 3a and 3c from 4-fluoroxanthone (CAS:[2839-51-2]).

b) (RS)-4-Fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 233 °C and MS: m/e = 379.2 ($M+H^+$) is prepared in accordance with the general method of example 3c from 4-trifluoromethyl-oxazol-2-ylamine and (RS)-4-fluoro-9-xanthene-carboxylic acid.

Example 8

(RS)-4-Fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 228 °C and MS: m/e = 379.2 ($M+H^+$) is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and (RS)-4-fluoro-9-xanthene-carboxylic acid.

Example 9

2,7-Difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 259 °C and MS: m/e = 397.1 ($M+H^+$), is prepared in accordance with the general method of example 3c from 4-trifluoromethyl-oxazol-2-ylamine and 2,7-difluoro-9H-xanthene-9-carboxylic acid (CAS:[188028-26-4]).

Example 10

2,7-Difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 232 °C and neg. ion MS: m/e = 395.1 ($M-H^-$), is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and 2,7-difluoro-9H-xanthene-9-carboxylic acid.

Example 11

3,6-Difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 265 °C and MS: m/e = 397.2 ($M+H^+$), is prepared in accordance with the general method of example 3c from 4-trifluoromethyl-oxazol-2-ylamine and 3,6-difluoro-9H-xanthene-9-carboxylic acid (CAS:[188028-37-7]).

Example 12

3,6-Difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 249 °C and MS: m/e = 379.2 ($M+H^+$), is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and 3,6-difluoro-9H-xanthene-9-carboxylic acid.

Example 13

(RS)-2-Chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide

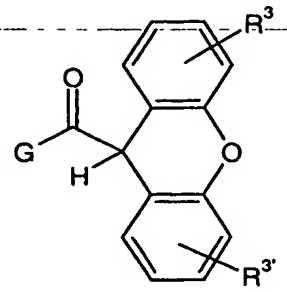
The title compound, white solid, m.p. 235 °C and MS: m/e = 395.2, 397.2 ($M+H^+$) is prepared in accordance with the general method of example 3c from 4-trifluoromethyl-oxazol-2-ylamine and (RS)-2-chloro-9H-xanthene-9-carboxylic acid (CAS:[188027-67-0]).

Example 14

(RS)-4-Chloro-9H-xanthene-9-carboxylic acid-(4-trifluoromethyl-oxazol-2-yl)-amide

The title compound, white solid, m.p. 212 °C and MS: m/e = 395.1, 397.1 ($M+H^+$) is prepared in accordance with the general method of example 3c from 5-trifluoromethyl-oxazol-2-ylamine and (RS)-4-chloro-9H-xanthene-9-carboxylic acid (CAS:[188027-87-4]).

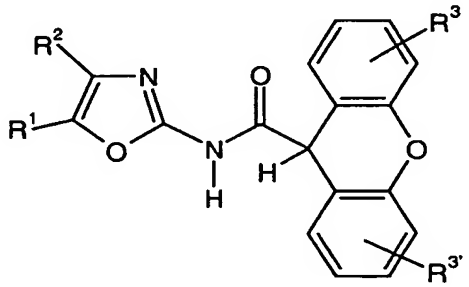
wherein one of R^1 and R^2 signifies trifluoromethyl, and the other one signifies hydrogen, with a compound of formula



III

wherein R^3, $R^{3'}$ signify, independently from each other, hydrogen or halogen, and G signifies chloro or hydroxy,

to obtain a compound of formula



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and, if desired,
converting a compound of formula I into a pharmaceutically acceptable salt.

17. A compound of formula I according to any one of claims 1 to 13, whenever prepared by a process according to claim 16.

18. Compounds of formula I according to claims 1 to 13 for the treatment and prevention of diseases.

19. The use of compounds of formula I according to claims 1 to 13 for the manufacture of medicaments for the treatment and prevention of diseases relating to the mGlu 1 receptor.

20. The use of compounds of formula I according to claims 1 to 13 in accordance with claim 19 for the manufacture of medicaments for the the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

21. The invention as herein before described.

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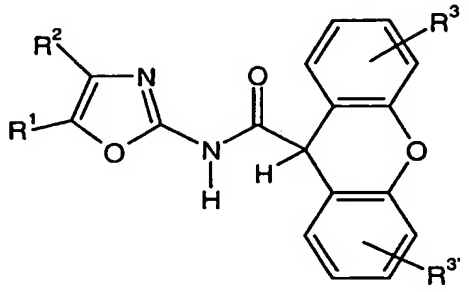
Claims

1. Compounds of the general formula



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wherein

one of R^1 and R^2 signifies trifluoromethyl, and the other one signifies hydrogen;

R^3, $R^{3'}$ signify, independently from each other, hydrogen or halogen;

as well as their pharmaceutically acceptable salts.

2. Compounds of formula I according to claim 1, wherein R^3 and $R^{3'}$ signify hydrogen.

3. Compounds of formula I according to claim 2, which compounds are selected from the group consisting of
9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide, and
9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide.

4. Compounds of formula I according to claim 1, wherein R^1 signifies trifluoromethyl and R^2 signifies hydrogen.

5. Compounds of formula I according to claim 4, wherein at least one of R^3 or $R^{3'}$ signifies halogen.

6. Compounds of formula I according to claim 5, wherein at least one of R^3 or $R^{3'}$ signifies fluoro.

7. Compounds of formula I according to claim 6, which compounds are selected from the group consisting of
2-fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide,
3-fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide,
4-fluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide,

2,7-difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide, and
3,6-difluoro-9H-xanthene-9-carboxylic acid (5-trifluoromethyl-oxazol-2-yl)-amide.

8. Compounds of formula I according to claim 1, wherein R^2 signifies trifluoromethyl and R^1 signifies hydrogen.

9. Compounds of formula I according to claim 8, wherein at least one of R^3 or $R^{3'}$ signifies halogen.

10. Compounds of formula I according to claim 9, wherein at least one of R^3 or $R^{3'}$ signifies fluoro.

11. Compounds of formula I according to claim 10, which compounds are selected from the group consisting of
2-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide,
3-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide,
3-fluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide,
2,7-difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide, and
3,6-difluoro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide.

12. Compounds of formula I according to claim 9, wherein at least one of R^3 or $R^{3'}$ signifies chloro.

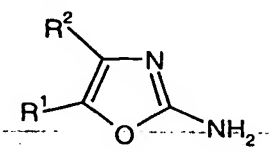
13. Compounds of formula I according to claim 12, which compounds are selected from the group consisting of
2-chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide, and
4-chloro-9H-xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide.

14. A medicament containing a compound of formula I accroding to any one of claims 1 to 13 and pharmaceutically acceptable excipients.

15. A medicament according to claim 14 for the treatment of diseases related to the mGlu 1 receptor.

16. A process for preparing a compound of formula I according to claim 1, which process comprises

reacting a compound of formula



II

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.